Attorney's Docket No. 1017751-000039

## IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

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| In re Patent Application of | ) | |
| Bruno Criere et al. | ) | Group Art Unit: 1618 |
| Application No.: 10/677,861 | ) | Examiner: Shirley V Gembeh |
| Filed: October 3, 2003 | ) | Appeal No.: ______________ |
| For: PHARMACEUTICAL COMPOSITION CONTAINING FENOFIBRATE AND METHOD FOR THE PREPARATION THEREOF | ) | |

## APPEAL BRIEF

**Mail Stop APPEAL BRIEF - PATENTS**
Commissioner for Patents
P.O. Box 1450
Alexandria, VA 22313-1450

Sir:

This appeal is from the decision of the Primary Examiner dated February 10, 2009 finally rejecting claims 72 and 76-78, which are reproduced as the Claims Appendix of this brief.

☐ A check covering the ☐ $ 270 ☐ $ 540 Government fee is filed herewith.

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The Commissioner is hereby authorized to charge any appropriate fees under 37 C.F.R. §§1.16, 1.17, and 1.21 that may be required by this paper, and to credit any overpayment, to Deposit Account No. 02-4800.

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## Real Party in Interest

The present application is assigned to Ethypharm. Ethypharm is the real party in interest, and is the assignee of Application No. 10/677,861.

## I. Related Appeals and Interferences

The Appellant's legal representative or assignee does not know of any other appeal or interferences that will affect or be directly affected by, or have bearing on, the Board's decision in the pending appeal.

## II. Status of Claims

Claims 72 and 76-78 are pending in the application, and stand rejected.

## III. Status of Amendments

All amendments have been entered.

## IV. Summary of Claimed Subject Matter

The subject matter of the instant claims is a method of reducing the "food effect" in the administration of drugs for the treatment of high blood levels of cholesterol, lipids, and triglycerides, which are associated with cardiovascular disease. The drugs are notoriously lipophilic, i.e., soluble in oil or fat, but insoluble in water. As such, they are not well absorbed in the digestive tract. To achieve therapeutic levels, clinicians administer a high dose and co-administer the drug with a high fat meal. However, high fat meals contribute to the condition under treatment and are disfavored. In the absence of a high fat meal, the drugs have poor bioavailability, and so are said to suffer from a "food effect."

The claimed subject matter includes methods of administration of such drugs that increase bioavailability, and as such diminish the food effect. This reduces reliance on co-administration of a high fat carrier and reduces the dose needed for therapeutic effect, thereby reducing cost and the likelihood of adverse side effects.

The claimed subject matter includes a method of reducing food effect by administering granules of a pharmaceutical composition comprising a neutral core, micronized fenofibrate, a surfactant and a binding cellulose derivative, and wherein the neutral core comprises a sugar, alone or mixed with starch; and the active layer comprises the micronized fenofibrate, the surfactant, and the binding cellulose derivative; and wherein the mass ratio of fenofibrate to binding cellulose derivative is between 5/1 and 15/1, and the binding cellulose derivative represents 5-12 % by weight of the composition.

## V. Grounds of Rejection to be Reviewed on Appeal

The sole independent claim, 72, stands rejected under §102(e) over Stamm et al. (USPN 6,074,670, hereinafter "Stamm")

Pending claims, 72 and 76-78, stand rejected under §103(a) over Stamm and Boyer (USPN 4,800,079) in view of US Department of Health and Human Services Food and Drug Administration Center for Drug Evaluation and Research (1997, hereinafter CDER), as evidenced by Munoz et al, Atherosclerosis, 110, S45-S48 (1994).

Claims 34, and 72-79 [*sic*; only claims 72 & 76-78 are pending] stand provisionally rejected for obviousness-type double patenting. Applicants will file an appropriate Terminal Disclaimer when the other rejections are resolved.

## VI. Argument

### *Stamm is Misconstrued and Lacks an Express Element*

Both prior art rejections misconstrue Stamm. The erroneous construction results in a missing element explicitly recited in the claims. As such, there is no anticipation; and, as the missing element is not found nor alleged to be in any of the secondary references, there is likewise no *prima facie* case of obviousness. Both rejections are improper and should be withdrawn.

The §102 rejection asserts, among other things, that Stamm teaches a pharmaceutical composition comprising micronized fenofibrate, a surfactant, and a binder of cellulose derivative. The rejection further asserts, erroneously, that "the hydrophilic polymer is from 5-40% by weight in a granular form." (citations omitted).

This latter assertion is wrong on at least two counts. First, Stamm does not teach a "pharmaceutical composition" as claimed having 5-40% by weight hydrophilic polymer, rather it describes a *suspension* to be used as a precursor in a process for manufacturing a pharmaceutical composition. Second, this precursor mixture that does have 5-40% by weight hydrophilic polymer is quite explicitly described as a suspension, and thus is not in "granular form."

Stamm does indeed teach a pharmaceutical formulation comprising micronized fenofibrate. And, as with the art in general, Stamm was in search of a formulation that would increase fenofibrate bioavailability and thereby reduce the food effect and lower the therapeutically effective dose. In this respect, Stamm supports the nonobviousness of the claimed invention in that it illustrates the long sought but unsolved need that existed within the art.

Stamm pursued an approach squarely at odds with that of the claimed invention. Stamm did not create a pharmaceutical formulation (as that term is used here) with 5-40% hydrophilic polymer. Rather, Stamm expressly teaches that the hydrophilic polymer must represent from 20 to 60% by weight, and preferably an even greater amount, i.e., 25-45% by weight. Col. 5, lines 4-6. Subsequently, Stamm teaches that "[T]he hydrophilic polymer represents preferably more than 25% by weight, based on the weight of (a)." Col. 5, lines 11-12. The component (a) is defined as the inert carrier and the fenofibrate, hydrophilic polymer, and, optionally, a surfactant. Col. 3, lines 12-20. It defines the composition as being that wherein "said hydrophilic polymer [is] making up at least 20% by weight of (a)." Col. 5, lines 18-19 (emphasis added). Thus, Stamm teaches formulations wherein at least one-fifth, and as much as nearly one-half, of the composition is hydrophilic polymer.

According to Stamm, to the extent the hydrophilic polymer contributes to increased bioavailability and water solubility, it does so by virtue of its "affinity toward water to dissolve therein and form a gel." Col. 4, lines 14-17. Stamm teaches that to achieve that effect, there must be at least 20% hydrophilic polymer in the formulation. It stands to reason that if the art teaches that the hydrophilic polymer increases bioavailability by enhancing its dissolution in water, that more is better. Thus, Stamm would have motivated one seeking to enhance or optimize the effect by increasing the amount of hydrophilic polymer.

In contrast, the instant claims recite a formulation wherein the hydrophilic polymer is substantially reduced from what Stamm teaches is a minimum quantity. Applicants' claims recite hydrophilic polymer at 5-12% by weight relative to the pharmaceutical formulation. This is only one-twentieth to about one-eighth of the weight of the formulation compared to Stamm's one-fifth to nearly one-half. Applicants have thus gone squarely against the express teaching of Stamm by using substantially less than the *at least 20%* hydrophilic polymer; and have likewise gone squarely against the direction in which the ordinary skilled worker would likely have gone if there were any motivation to further modify the prescribed amount of hydrophilic polymer.

The express teaching of Stamm requiring *at least 20%* hydrophilic polymer forecloses reliance on that reference as an anticipatory reference. Likewise, it forecloses reliance on Stamm as suggesting the claimed invention without an art-recognized express teaching from another reference discrediting Stamm in that specific respect.

The rejection asserts that Stamm teaches a pharmaceutical formulation wherein the hydrophilic polymer is from 5-40% by weight in a granular form. As stated above, this is incorrect at least twice over. As shown above, Stamm repeatedly and expressly teaches that the hydrophilic polymer must be *at least 20%* by weight of the formulation, and is preferably greater than 25%. Thus, Stamm does not teach or suggest the preparation of a pharmaceutical formulation having 5-40% hydrophilic polymer.

Stamm does appear to recite the preparation of a *suspension* having 5-40% hydrophilic polymer. However, that *suspension* is not a pharmaceutical formulation as claimed, nor is it in granular form. Rather, the suspension is something that is used in a preliminary process step on the way toward fabricating a pharmaceutical formulation, which, according to Stamm, must have at least 20% by weight hydrophilic polymer.

Stamm explains the relationship of *suspension* to the ultimate *composition*:

> The composition according to the invention is prepared by a novel process comprising spraying a suspension of the active ingredient in a micronized form in a solution of a hydrophilic polymer and, optionally, a surfactant, onto the inert core.

col. 5, lines 31-35.

Stamm later states:

> The significant starting product is the *suspension* of the active ingredient. This *suspension* is prepared by putting the micronized active ingredient *into suspension in a solution* comprising the hydrophilic polymer and, optionally, a surfactant, in *solution in a solvent.*

Col. 6, lines 16-20 (emphasis added).

In the two paragraphs immediately following, Stamm describes the requisite concentrations of active ingredient and hydrophilic polymer in the *suspension*. Stamm states "[T]he hydrophilic polymer concentration *in the suspension* is from 5 to 40% by weight, preferably 10 to 25%." Col. 6, lines 36-37 (emphasis added).

Stamm also teaches that the suspension is applied to the neutral microgranules by, e.g., fluidized-bed granulation technique. Col. 5, lines 46-48. The fluidized-bed granulation technique is a means for coating a substrate by applying a coating solution and drying the solution by removal of solvent. *See, e.g.,* Remington's Pharmaceutical Sciences, Gennaro, A.R., Ed., p. 1641, 17th ed. (1985). One skilled in the art would have known that Stamm applies the suspension to a substrate (inert cores), and then dries the suspension; and that the relative concentrations of constituents would have changed substantially by the loss of solvent and addition of inert core. The relative concentration of the constituents of a coating suspension would not be the same as the relative concentration in the resulting pharmaceutical composition, and thus the description of a *suspension* having 5-40% (weight) hydrophilic polymer is irrelevant to the concentration of the hydrophilic polymer in the dried, granulate pharmaceutical composition.

Stamm's Example 1 is illustrative. Stamm describes compounding a suspension for spraying on inert cores. The suspension is: sodium lauryl sulfate, 7 g; demineralized water, 1750 g; micronized fenofibrate, 350 g.; PVP, 350 g. The hydrophilic polymer (PVP) is about 14% by weight of the *suspension*. However, to make the pharmaceutical composition, the solvent (water) is removed and the suspension is applied to 400 g lactose cores. The resulting pharmaceutical composition is 31% PVP. This is consistent with Stamm's preferred range of greater than 25% hydrophilic polymer in the solid pharmaceutical composition. Stamm, col. 5, lines 11-12.

The outstanding rejections fail to support a novelty rejection, and fail to support a *prima facie* case of obviousness. In both instances, an express element of the claims is missing. Applicants' claims require, among other things, neutral cores coated with 5-12% by weight of a binding cellulose derivative based on the weight of the pharmaceutical composition. It is asserted, erroneously, that Stamm teaches or suggests a pharmaceutical composition of granules having 5-40% hydrophilic polymer. Instead, Stamm teaches the formulation of a *suspension* having 5-40% hydrophilic polymer.

Among other things, the Stamm *suspension* is distinct from the formulation of the claimed method in that it is not in the form of *granules* (it being a suspension); and the suspension contains no neutral cores.

Further, in reference to the Stamm pharmaceutical composition most analogous to that of the claimed method, Stamm requires *at least 20%*, and *preferably greater than 25%* by weight hydrophilic polymer. This is distinct from the composition administered in the claimed methods (i.e., 5-12% by weight binding cellulose derivative).

As the alleged anticipating reference (Stamm) lacks several of the express elements of the rejected claim, the reference fails to anticipate each and every element of the claim. Accordingly, the novelty rejection is improper. Reconsideration and withdrawal of the rejection is respectfully requested.

Likewise, the Stamm reference fails to suggest the missing elements, and none of the secondary or supporting references has been shown, or even alleged, to teach or suggest the missing elements. Accordingly, there is no *prima facie* case of obviousness. Reconsideration and withdrawal of the obviousness rejection is respectfully requested.

### *The Secondary References Are Also Misconstrued*

Even ignoring the foregoing deficiencies of Stamm, the obviousness rejection fails as the secondary references do not provide even so much as a teaching or suggestion of the elements acknowledged as missing from Stamm.

#### *Boyer*

The rejection asserts that Boyer teaches administering micronized fenofibrate to patients suffering from high triglycerides. Applicants do not contest the known use of micronized fenofibrate for treating high blood levels of triglycerides. Applicants expressly acknowledged those developments in the Background and Description of Related Art. Specification, ¶0002 & 0009. However, Applicants' Detailed Description of the Invention states that the methods and formulations disclosed provide greater bioavailability than the prior art, and that the greater bioavailability is independent of the food effect. Specification, ¶0018. Moreover, the instant methods and formulations avail greater bioavailability than prior art formulations containing substantially greater doses of micronized fenofibrate. ¶0014.

As with Stamm, however, Boyer is misconstrued. The rejection erroneously asserts that Boyer teaches administering micronized fenofibrate having an inert core comprising 12.5% cellulose binder. This is not what Boyer teaches. The commonly owned Boyer patent teaches dampening inert cores "with an alcohol solution containing 12.5% by weight of a methacrylic polymer (95% alcohol). The grains become damp and sticky. Fenofibrate powder is then projected onto them…." Boyer, col. 2, lines 52-56.

The Boyer description of a 12.5% polymer concentration is measured relative to the alcohol solution; not the recited formulation of: inert core, fenofibrate, surfactant, and binding cellulose derivative. One of ordinary skill in the art would immediately appreciate from Boyer that the concentration of methacrylic polymer in the alcohol solution does not correlate to the concentration of cellulose binder in the ultimate pharmaceutical formulation actually administered. Thus, contrary to the assertion of the rejection, Boyer does not teach a fenofibrate formulation having 12.5% binding cellulose derivative.

### *CDER*

The CDER reference also fails to provide the asserted teaching or suggestion. CDER is cited as curing the acknowledged deficiency of Boyer of feeding a patient a high fat containing meal. Applicants do not claim such a step. Quite the opposite. Applicants' claims are clearly directed to a method of treatment that eliminates the need for such a high fat containing meal. The well known "food effect", long since associated with fenofibrate, and acknowledged by Applicants throughout their specification, dictates that increased bioavailablity of fenofibrate requires co-administration of a high fat meal. This is consistent with the lipophilic character of fenofibrate, i.e., it is more readily dissolved in fats and oils.

The CDER reference likewise acknowledges the existence of food effect in certain therapeutics, and offers a brief discussion of its causes and effects. It provides, among other things, guidance for the industry for conducting bioavailability and bioequivalence studies for oral dosage forms. However, the reference does not address how one reduces or eliminates the food effect; merely how it is to be measured.

Indeed, the rejection asserts that "CDER gave teachings on how to conduct food effect bioavailability." *Office Action,* Feb. 10, 2009, p. 6. However, nowhere does the rejection even assert that the reference teaches or suggests how to *eliminate* that food effect, and Applicants are unable to find such a teaching or suggestion.

Elsewhere, it is argued that "In other words, reducing the food effect via treating hyperlipidemia occurs through administering fenofibrate" *Office Action,* Feb. 10, 2009, p. 7. This is also incorrect, it is wholly unsupported, and it ignores teachings throughout the art, e.g., Boyer and Stamm, acknowledging fenofibrate's low water solubility and poor uptake from the digestive tract. Thus, fenofibrate's poor bioavailability and variable uptake is a longstanding and heretofore unsolved problem within the art.

That fenofibrate suffers from a food effect is well known, and acknowledged by Applicants. Applicants do not assert that they discovered this phenomenon, nor do they assert an exclusive right to means for measuring or assessing it. In such a case, the CDER reference might have had relevance. Instead, Applicants claim a method for eliminating food effect by, among other things, administering a novel and nonobvious fenofibrate formulation having substantially greater bioavailability than prior art formulations.

*Munoz*

Finally, it is asserted that Munoz cures the collective deficiencies of Stamm, Boyer, and CDER by teaching formulations that reduce food effect. However, Munoz, a 1994 reference, is directed only to micronized fenofibrate formulations as a means for increasing bioavailability. Although this expedient is represented as improving fenofibrate bioavailability, the reference nonetheless lacks several elements of the instant claims.

Applicants acknowledged the existence of micronized fenofibrate in the prior art, as well as other advances such as co-micronization. However, Applicants do not rely upon micronized fenofibrate alone. Rather, Applicants have recited numerous claim elements that have been shown to be found in Munoz. Neither Munoz nor any of the other cited references, whether alone or in combination, teaches or suggests the methods claimed here.

For at least the foregoing reasons, the outstanding rejections are improper, and fail to make a *prima facie* case. Applicants respectfully request reconsideration and withdrawal of all outstanding rejections in favor of a Notice of Allowability on the merits.

## VII. Claims Appendix

See attached Claims Appendix for the claims on appeal.

## VIII. Evidence Appendix

Not applicable.

## IX. Related Proceedings Appendix

Not applicable.

Respectfully submitted,

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## VIII. CLAIMS APPENDIX

**The Appealed Claims**

1. - 33. (Canceled)

34. - 71. (Canceled)

72. (Previously Presented) A method of reducing food effect when treating hypertriglyceridemias and/or hypercholesterolemias and/or hyperlipidemias in a patient in need thereof comprising administering to said patient a therapeutically effective amount of a pharmaceutical composition comprising micronized fenofibrate, a surfactant and a binding cellulose derivative, wherein said composition is in the form of granules comprising:

(a) a neutral core; and

(b) an active layer, surrounding the neutral core;

wherein said neutral core comprises a sugar or a sugar mixed with starch; said active layer comprises the micronized fenofibrate, the surfactant, and the binding cellulose derivative; and wherein the mass ratio of said fenofibrate to said binding cellulose derivative is between 5/1 and 15/1, and said binding cellulose derivative represents between 5 and 12 % by weight of the combined neutral core, and the fenofibrate, surfactant and binding cellulose derivative of the active layer.

73. - 75 (Canceled)

76. (Previously Presented) The method of claim 72, wherein said patient is fed a high fat containing meal and the bioavailability of fenofibrate administered to said patient is equivalent to when said patient has fasted.

77. (Previously Presented) The method of claim 72, wherein said patient is fed at least 800-1000 calories, 50% of which are from fat, and the bioavailability of fenofibrate administered to said patient is equivalent to when said patient has fasted.

78. (Previously Presented) The method of claim 72, wherein said patient is fed a therapeutic lifestyle change diet and the bioavailability of fenofibrate administered to said patient is equivalent to when said patient has fasted.

79. (Canceled)

## IX. EVIDENCE APPENDIX

## X. RELATED PROCEEDINGS APPENDIX